REMARKS

Claims 9 and 11 are in this application.

The examiner rejects Claims 9 and 11 as being obvious in view of US 5,629,327; Masiero *etal.*, and US patent 5,696,092 *et al.* This is respectfully traversed for the reasons explained below.

Applicants respectfully disagree with the examiner's position that the claims are obvious over the cited references. The present invention relates to the use of thalidomide *per se* for treating hepatocellular carcinoma in a specific amount of 30 to1200 mg. Examples 2 and 3 illustrate a thalidomide treatment with 100mg to patients having hepatocellular carcinoma, and show that oral administration of a capsule containing thalidomide as a single principle ingredient significantly reduces the tumor size and/or the serum level of alpha-fetoprotein in the patients.

US 5,629,327 is directed to a group of compounds (including thalidomide) having anti-angiogenesis activity. The patent illustrates the use of thalidomide in the treatment of corneal neovascularization and suggests some diseases involving undesired angiogenesis, such as rheumatoid and hemangiomas, are treatable by thalidomide. This citation discloses a long list beginning at col. 1, line 21 of conditions and diseases associated with regulated or unregulated angiogenesis. Since no examples of solid tumors are given in the citation and there is no specific disclosure concerning the use of thalidomide to treat hepatocellular carcinoma in the citation, the citation does not provide one of skill in the art with a reasonable expectation of success that thalidomide can be used to treat hepatocellular carcinoma given the number of conditions associated with angiogenesis.

Masiero *et al.* discloses that thalidomide is currently tested in phase II of clinical trials for prostate cancer, glioblastoma and breast cancer. However, the citation does not suggest nor imply the

treatment of hepatocellular carcinoma by 30 to 1200 mg of thalidomide as claimed in this application. It is well known in the art that the treatment of a type of cancer does not mean that the same treatment will work for all types of solid tumors. As shown in the article previously submitted (Paragraph 9 of the article obtained from the website www.netwellness.com/healthtopics /cancer/solid.cfm), some tumors of the breast, uterus and prostate grow faster in the presence of certain hormones. Based on the teachings of the article, and because of the differences in sensitivity to sex hormones of the breast and prostate hormones, the disclosures in Masiero of treatment of breast and prostate cancer do not teach treatment of hepatocellular carcinoma with a specific amount of 30 to 1200 mg nor does it suggest with a reasonable expectation of success that hepatocellular carcinoma can be treated using thalidomide.

US 5,696,092 relates to methods and compositions that prevent or inhibit metastases of cancers of epithelial cell origin, especially human prostate cancers. The patent focuses on the use of compounds that inhibit phospholipase A_2 or arachidonic acid released by cells of a tumor for preventing metastasis of the tumor. In particular, uteroglobin is taught in the citation. The citation neither discloses the use of thalidomide nor suggests that anti-angiogenesis agents can function as uteroglobin. It is noted that claims 1, 4, 5 and 6 of the citation particularly exclude the use of anti-angiogenesis agents. The fails to teach that anti-angiogenesis agents (such as thalidomide) are suitable for preventing metastasis of a cancer of epithelial cell origin especially hepatocellular carcinoma.

Considering all of the references together, it is clear that there is no combination of references that leads to the claimed invention. (**In re Fine** 13 USPQ 2d 1071.) See also **Panduit Corp. v. Dennison Manufacturing Co.** 227 USPQ 337 (Fed. Cir. 1985) where it was stated:

It is impermissible to first ascertain factually what applicants did and then view the prior art in such manner as to select from the random facts of the art only those which may be modified and

then utilized to reconstruct [the claimed] invention from such prior art. In arguing that a claimed invention is obvious, it is, of course, possible to combine teachings from a number ofdifferent documents. In order to do this, however, there needs to be some basis for reading the documents together.

The Federal Circuit summarized its prior case law on the question of the appropriateness of combining prior references to reach a conclusion of obviousness in **Ruiz v. A. B. Chance Co.** (234 F.2d 654, 57 USPQ2d 1161 (2000)).

The reason, suggestion, or motivation to combine may be found explicitly or implicitly: 1) in the prior art references themselves; 2) in the knowledge of those of ordinary skill in the art that certain references, or disclosures in those references ,are of special interest or importance in the field; or 3) from the nature of the problem to be solved leading inventors to look to references relating to possible solutions to that problem. While the references need not expressly teach that the disclosure contained therein should be combined with another, the showing of combinability must be clear and particular. (Internal citations omitted.)

To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, and not based on applicant's disclosure.

There is no reason, suggestion or motivation in the combination of the cited references to use

thalidomide to treat hepatocellular. There is no combination of these references that disclose the use of thalidomide to treat a solid tumor. The only reference that discloses liver cancer in US patent 5,696,092. This patent refers to use of compositions that inhibit arachidonic acid release to prevent or inhibit metastases of cancers of epithelial cell origin. The only examples refer to prostate cancer cell lines and in these examples uteroglobin was tested against these cell lines. Attached are descriptions of uteroglobin and thalidomide which clearly illustrate the differences between the two compounds. Given the differences between the two compounds it would not be expected that one skilled in the art would be motivated to use thalidomide instead of uteroglobin. Further as explained above, given the differences between different types of cancers, there is no expectation of success that a drug that is used in the treatment of breast and prostate cancer can be used to treat liver cancer. Furthermore, given the differences between uteroglobin and thalidomide, there is no suggestion nor would it be expected that one skilled in the art would consider Masiero in combination with US patent 5,696,092. As stated above in reference to US patent 5,628,327, as there are no examples of solid tumors in the reference and there is no specific disclosure concerning the use of thalidomide to treat hepatocellular carcinoma in the patent, given the differences between hepatocellular carcinoma and corneal neovascularization and thalidomide and uteroglobin, there is no combination of the cited references that would make the claimed invention obvious.

Furthermore, the applicant obtained a drug license for thalidomide (Trade name: Thado®) for theindication of Erythema Nodosum Leprosum (ENL) from the Department of Health (DOH) in Taiwan. Ithas been shown that thalidomide is effective in treating hepatocellular carcinoma in a number of recentinvestigations. Furthermore, the sales amounts of thalidomide in the treatment of hepatocelluar carcinoma increased seven-fold within five years (from 2002 to 2006) (see Enclosure 1). In practice, hospitals (ordoctors) have to file a special application for Thado® for patients with the DOH to get approval because of the birth defect concern (see Enclosure 2 and the specification, [0001]). In such applications, hospitals (doctors) should describe why the patients

need Thado®, the dosage every day, the therapeutical period,the capsule usage amount, and provide the patient's agreement, therapeutical plan and other references (see Enclosure 3 and 4, as examples for the special application process). Even though the application process for using Thado® is complicated, many doctors decided to use thalidomide to treat liver cancerwhen they found other drugs or therapeutic regimens (such as transcatheter arterial chemoembolization, TACE) were ineffective. The applicant believes that the above-mentioned facts can be used as the secondary consideration of non-obviousness.

Given the above, the above-mentioned citations, either alone or in combination, cannot render the invention obvious. The rejections under 35 USC 103 should be withdrawn.

Accordingly it is respectfully submitted that the present application is in condition for allowance and favorable consideration is respectfully requested.

Respectfully submitted,

JANET I. CORD
LADAS & PARRY
26 WEST 61ST STREET
NEW YORK, NEW YORK 10023
REG. NO.33778 (212)708-1935